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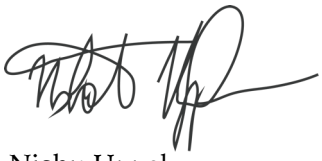
Dear readers,

We are thrilled to present this fourth issue of the Harvard Medical Student Review (HMSR), which represents an incredible diversity of thought and illumination of current issues within the field of medicine, contributed by medical and graduate students throughout the U.S. The HMSR has recently re-established its activity after a hiatus in leadership transitions, with this being the first issue published since 2015. As the new executive board, we have generated a goal of producing content that is both compelling and timely to the medical community. We hope that you will find the articles presented here as engaging as we did.

This journal is only possible from the contributions of a large and passionate team, including Associate Editors who strengthened the quality of every submission through peer-review, Art Editors who created original works for each article, and prior HMSR executive board members who continue to serve as sources of advice and inspiration. Finally, we would like to thank all of our faculty and strategic advisors for their input this year, especially Gina Vild at the Office of Communications and External Relations for her generous funding to support our organization's growth.

Sincerely,

Kathy Wang
Editor-in-Chief



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About HMSR

The Harvard Medical Student Review (HMSR) is student-founded, student-managed, and student-administered under the guidance of faculty and staff. Its mission is to provide a platform for students to contribute to important issues facing health and medicine through a variety of formats, including scholarly articles, editorials, and original artwork. Contributions are invited from the Harvard medical, dental, and public health schools, the rest of Harvard University, and other medical schools.

The articles represent the views and opinions of the original authors and does not necessarily represent the views or opinions of the Harvard Medical Student Review or Harvard Medical School.

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The Paradox of South Asian Disparities in Medicine

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As medical students of South Asian descent training in the Boston area, we are fortunate to have many role models. We are lucky to be taught and supported by phenomenal faculty, residents, and fellow medical students, many of whom hail from similar backgrounds as we do. Seeing people who look like us, share our culture or religion, or speak the same language as we do allows us to envision ourselves practicing as physicians in the near future. It is particularly inspiring that so many thought leaders in American medicine are of South Asian descent, including physician-writers Atul Gawande and Siddhartha Mukherjee, physician-researchers Ashish Jha and Amitabh Chandra, government leaders Seema Verma (CMS Administrator) and Vivek Murthy (former Surgeon General), and so many others. While this level of representation is encouraging for budding medical students like ourselves, to be of South Asian descent in medicine is to face a troubling paradox.

Defining the Paradox

It has been well established that the recent surge in immigration from South Asian countries (e.g. India and Pakistan) is in part attributed to domestic needs for healthcare practitioners coupled with an immigration pipeline facilitated by the Immigration and Naturalization Act of 1965, which dismantled quotas based on countries of origin that had previously limited South Asian immigration [1]. As a result of this surge in immigration, the proportion of United States physicians identifying as Indian or Pakistani (4.8%) is greater than the proportion of the general population identifying as South Asian (1.2%), an expected result that has led some to use the term "overrepresented" when describing the representation of South Asian people in our healthcare workforce [2,3,4]. We might expect that physicians, as highly educated and socioeconomically advantaged members of society, would enjoy better health, an assumption that has been corroborated by the Centers for Disease Control and Prevention (CDC), which reported that those in higher income and education levels experience chronic diseases at lower rates [5]. However, despite a greater representation in the physician workforce, the South Asian American population paradoxically experiences higher rates of cardiovascular disease compared to white Americans across several metrics.

Recent epidemiological research is beginning to shed light on this paradox. A study of Asian Indian physicians and their family members revealed that the age-adjusted prevalence of myocardial infarction and/or angina in Asian Indian men was 7.2%, approximately three times greater than that of white men [6]. The prevalence of type 2 diabetes mellitus among Asian Indians was more than seven times greater than that among white Americans, despite lower rates of cigarette smoking, obesity, and hypertension in the Asian Indian population [6]. These disparities cannot be completely explained by hyperlipidemia, part of the trifecta of risk factors

(i.e. hypertension, hyperlipidemia, and smoking) that has predictive value in the US Caucasian population [7]. Obesity also does not predict cardiovascular disease and insulin resistance in Asian Indians in the way it does in white counterparts; after controlling for age and body fat percentage, it appears that even among young, healthy Asian Indians, higher levels of inflammatory markers may predispose to a pro-inflammatory state that increases their risk for these conditions [8].

South Asian men and women are more susceptible to heart attacks, and these attacks are deadlier than those experienced by any other ethnic group [9]. Nearly one in three South Asians will die from heart disease before the age of 65. While a constellation of risk factors for this phenomenon has been suggested, they are compounded by the absence of specific testing for lipid/inflammatory biomarkers. This is especially true for younger South Asians, despite data demonstrating that even during childhood, South Asians have elevated blood levels of cholesterol and lipoproteins.

TARGETED INTERVENTIONS

South Asians have received relatively little attention in the disparities literature, a surprising trend given the overrepresentation of South Asians in the medical profession. Though the roles of nutritional epigenetics, exposure to environmental pollutants, lifestyle patterns, microbiome differences, and psychological stressors have all been posited as contributors to South Asian health disparities, there is a need to further explore the corresponding modifiable risk factors [10]. While recent research is uncovering the nuances of South Asian health at the population level, it is important to note that some key findings have long been recognized. For example, higher rates of coronary artery disease among Asian Indians have been reported in the literature for nearly 30 years. However, few tar-

geted interventions for South Asian Americans currently exist [11].

The Stanford South Asian Translational Health Initiative (SSATHI) is one of few programs geared towards tailoring treatment plans for cardiovascular health in South Asians, taking into account dietary and cultural factors to provide holistic healthcare [12]. The Memorial Sloan Kettering Cancer Center (MSKCC) recently developed a similar South Asian Health Initiative (SAHI). This initiative works in conjunction with faith-based and community organizations to sponsor health fairs where South Asians can receive free blood pressure, cholesterol, and diabetes screenings, and also learn about low-cost services and health insurance assistance to enable better access to preventative care [13].

Although these programs are examples of necessary first steps in addressing health disparities, they have yet to be replicated at scale nationwide, and they fall short of the personalized tailoring that is needed to more meaningfully address these disparities. While culturally customized models for prevention, diagnosis, and treatment are still in development, even those that have been proposed as policy recommendations are not widely adopted. For instance, South Asians often do not engage in conversations with their providers about complementary medicine, even though most members of the South Asian community are explicitly aware of the usage of alternative remedies [14]. Interventions targeted towards improving South Asian health also offer value to others seeking to tackle disparities in other ethnic and religious populations, who may face similar cultural and institutional barriers.

Studies show that targeting interventions according to population-level disparities can be effective. For instance, the Indian Diabetes Prevention Programme (IDPP), a 3-year randomized controlled trial conducted in India, introduced lifestyle modification techniques and metformin to individuals at high risk for developing diabetes in order to reduce rates of progression from impaired glucose tolerance to diabetes. In addition to improving patient outcomes, the program demonstrated cost-effectiveness even in the short term and even in settings with limited health resources [15]. In the United States, the ongoing transition of our health system towards value-based care creates ample opportunity for investment in similar cost-effective interventions for the South Asian immigrant population. Doing so would allow us to provide tailored care to a population with significant and unique risk factors while also expanding our understanding of how disease manifests differently in people of distinct origins.

While programs such as the IDPP provide learning opportunities for American medicine, the ability to implement these interventions will require partnership with South Asian community organizations to overcome challenges posed by cultural beliefs and practices concerning health, as well as commensurate efforts by the biomedical research institution to uncover new diagnostic and treatment modalities. An active collaborative comprised of these stakeholders and buy-in from clinicians, researchers, and the South Asian community at large offers the best chance of pioneering targeted interventions and proving scalability for fellow advocates seeking to address these striking health disparities.

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VIEWPOINT
Health Policy

Deportation and Deprivation: How Discriminatory U.S. Immigration Policy Restricts the Right to Healthcare Access for Latinx Citizen-Children

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Recent detention and deportation policies in the U.S. target undocumented Latinx immigrants and engender an environment of fear. U.S. citizen-children in mixed-status Latinx families are impacted in the form of decreased healthcare accessibility. The barriers to care faced by this disproportionately victimized population constitute a human rights violation.

INTRODUCTION

In recent decades, U.S. immigration enforcement policy has become increasingly punitive with an intensified focus on the removal of undocumented immigrants [1]. A greater proportion of removals are carried out by the U.S. Immigrations and Customs Enforcement (ICE) agency and increasingly take place in the nation's interior rather than in border regions [2]. This evolution in tactics has led to greater rates of detention and deportation among undocumented Latinxs, who comprise the majority of the unauthorized migrant population [3]. The criminalization of unauthorized status and perception of ethnically charged immigration enforcement policy have contributed to a growing sense of fear in Latinx communities [4].

While some may laud the efforts to remove this increasingly polarizing population from within our nation's borders, the consequences of deportation and detention have proven detrimental for a vulnerable and oft-forgotten group: Latinx citizen-children, or U.S.-born children of undocumented

immigrant parents. Nearly six million citizen-children live in mixed-status households with one or more undocumented relatives [5]. For every two adults deported, one citizen-child is directly affected [6]. Between July 2010 and September 2012, nearly 205,000 parents of citizen-children were deported [7]. The same policies that claim to protect Americans from illegal immigrants actually expose American citizen-children to a litany of stressors and impede them from enjoying the freedoms to which they are entitled. This paper highlights how deportation and detention policies negatively affect the health of Latinx citizen-children of mixed status familes by fomenting community-wide fear that hinders access to and utilization of public services. The disproportionate damage inflicted upon this targeted minority constitutes a violation of the right to healthcare access and freedom from discrimination specified in the Universal Declaration of Human Rights (UDHR).

THE DISCRIMINATORY NATURE OF RECENT IMMIGRATION POLICY

Though all migrant communities feel the effects of deportation policy, Latinx populations have been disproportionately targeted. Indeed, Latinxs have faced ethnically driven violations of their rights for decades, as in the arrest that led to the 1974 Supreme Court case United States v. Brignoni-Ponce. California officers arrested and charged Humberto Brignoni-Ponce with knowingly transporting immigrants; however it was found that the officers had targeted him solely because he appeared to be of Mexican descent—a violation of the Fourth Amendment right of protection from unreasonable search and seizure [8]. Though the court ruled that the appearance of Mexican ancestry was not legal ground to stop a vehicle and demand proof of citizenship, the incident exposed the leeway that non-federal agencies gave themselves in apprehending and charging suspected migrants.

Over the past two decades, a flurry of deportation-centered policies has reignited this debate by extending deportation duty to non-federal agencies. Over 1,500 new pieces of immigration legislation were passed by states between 2005 and 2011, many of which pass on the authority to apprehend and arrest suspected migrants from federal bodies to state and local forces. Colorado's 2006 Senate Bill 90 requires state and local police forces to report undocumented arrestees to ICE. Arizona's SB 1070 authorizes a "show me your papers" policy that requires immigrants to carry proof of citizenship and allows law enforcement to demand this documentation, provisions upheld by the US Supreme Court in Arizona v. United States [9]. A policy known as the Secure Communities enacted in 2008 also strengthens the ability of local law enforcement to act on behalf of federal immigration agencies [10]. In January 2017, President Donald Trump issued a series of executive orders aimed at increasing deportation of unauthorized immigrants regardless of prior criminal convictions. He called for the hiring of 10,000 immigration officers and authorized state and local law enforcement to carry out these duties [11].

As rising detention and deportation numbers coincide with deputizing of state and local forces, studies show that Latinx populations are disproportionately victimized. Mexican immigrants, who comprise 58% of unauthorized U.S. residents, accounted for 73% of those forcibly removed by Homeland Security forces in 2010 [12]. According to a 2011 report by the Warren Institute on Law and Social Policy at the University of California at Berkley regarding the 2008 Secure Communities Act, "Latinos comprise 93% of individuals arrested through Secure Communities though they only comprise 77% of the undocumented population in the United States" [10]. The same report revealed that 3,600 individuals apprehended by ICE through the program were actually U.S. citizens mistakenly identified as undocumented due to poorly updated naturalization registries. During an April 2018 raid of a Tennessee meat-processing plant, ICE forces detained 86 predominantly Mexican immigrants, the largest single workplace raid in a decade [13].

The emphasis on forcible deportation has impacted the broader Latinx community, from undocumented and documented migrants to established American families with Latino origins. In a study of self-reported feelings of discrimination in Los Angeles, Landale et al. revealed that native-born young Latino men are more likely to feel mistreated by


Artist: Jonnell Small

authority figures, including police, than their undocumented counterparts [14]. Similar results have been reproduced in Durham, North Carolina [15], indicating that interactions between police and the Latinx community engender feelings of ethnic discrimination across generations regardless of documentation status. In a cross-sectional analysis of Latinxs nationwide, Almeida et al. found that the perception of discrimination is correlated with the strength of anti-immigrant policies by state, especially among third-generation Latinx immigrants [16]. It takes no stretch of the imagination to postulate that feelings of persecution among Latinxs are in response to the targeting of their community by immigration forces.

The disproportionate effect of detention and deportation policies on Latinx populations clearly evinces an environment of discrimination that violates Article 7 of the UDHR as adopted by the United Nations, which states, "all are equal before the law and are entitled without any discrimination to equal protection of the law," [17]. The continued influx of migrants may be cited as reason for passage of more punitive policies. This alone would not be a violation of human rights. Statistics showing greater rates of detention and deportation among Latinx immigrants, however, suggest that this population is being unfairly affected. Latinx immigrants are being targeted and removed more than any other demographic, leaving behind a community-wide fear of discriminatory authorities.

The consequences of this fear include restricted access to healthcare for Latinx citizen-children. Were the effects felt evenly by citizen-children across all migrant populations, recent deportation policies could be perceived as cruel but would remain ethnically indiscriminate. The reality, however, is that the U.S. government has implemented tactics that subject its own Latinx citizens to unfair and damaging health effects based on their cultural backgrounds. The perception of discrimination is not without merit given the record of ICE and legislation like Secure Communities. Though this targeted legislation itself infringes upon the right to freedom from discrimination, its downstream consequences for citizen-children violate a separate article of the UDHR altogether.

THE EFFECT OF POLICY CHANGES ON HEALTH

Removing a child's parent from the household threatens lasting consequences on a child's quality of life resulting from unexpected loss of family income, poor relationships with fathers due to higher rates of male deportation, and emotional insecurity [18]. In the case of Latinx citizen-children, detention and deportation have a measurable negative impact on health and wellness. Latinx citizen-children affected by forced parental removal were found to report more symptoms of attention deficit and hyperactivity disorder (ADHD). Rates of depressive symptoms were also higher under these circumstances when compared to citizen-children whose undocumented parents are not under investigation or do not have a history of detention or deportation [19]. Rojas-Flores et al. described increased parent-reported rates of post-traumatic stress disorder (PTSD) symptoms in citizen-children who experience separation from a parent either through detention or deportation [3]. Corroborating what parents report, clinicians measured poorer overall functioning among these subjects using the Child and Adolescent Functional Assessment Scale (CAFAS). This holds true when compared to citizen-children of legal permanent resident parents as well as citizen-children of undocumented parents who have not faced forced parental removal. Evidence abounds demonstrating the negative health impact delivered to citizen-children when immigration law is enforced via detention and deportation.

Though these findings are significant, the direct negative health outcomes experienced by citizen-children are not sufficient to label deportation and detention policy a human rights violation. One may expect a child whose parent is forcibly removed from the home to suffer mental health consequences, whether that parent is a citizen criminal who has been incarcerated or an unauthorized immigrant who has been detained or deported. In both cases, the parent has violated the law and may be expected to face certain consequences. This paper, however, seeks to argue that recent immigration policies have moved beyond punishing those guilty of violating immigration law. They have sewn disproportionate panic among the local Latinx community, leading to

restricted access to healthcare for a group of vulnerable Americans.

The Effect of Policy Changes on Healthcare Accessibility

By removing undocumented Latinxs, punitive immigration policies alienate citizen-children not only from their parents, but also from the benefits to which they are entitled as Americans. Healthcare usage and social service access have been shown to be compromised in communities fearing deportation. In a focus group project on immigrant populations, Hacker et al. found that both documented and undocumented subjects reported reluctance to share personal information for insurance applications because they believed that the U.S. Immigration and Customs Enforcement (ICE) may apprehend this data and use it against them or a family member [20]. In the same study, interviewed participants also pointed to a fear of deportation as a reason for missing healthcare appointments. Other research shows that although undocumented children experience the greatest reduction in frequency of visits to dental care visits and public assistance enrollment, a disparity also exists between children of citizen mothers and citizen-children of noncitizen mothers [21]. This suggests that access to health resources for entitled Americans may be limited by the concern for removal of a parent, even if that parent is not the individual seeking the service.

Given regional differences in immigration policy and rates of migrant removal, recent studies have quantified deportation risk and used it to predict enrollment in federal health programs. Medicaid enrollment is negatively correlated with the risk of deportation in mixed-status Mexican families [22]. The risk of deportation, in this case, is a jurisdiction-specific measure of likelihood of deportation given the estimated number of unauthorized immigrants within the area and the number of unauthorized immigrants deported from that area. Vargas & Pirog also analyzed deportation risk as compared with enrollment in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), a program over 40 times more likely to be utilized by mothers in mixed-status families of Mexican origin than U.S.-born white mothers [23]. Once again, risk of deportation was negatively associated with WIC enrollment when holding constant the mother's age, education, marital status, economic hardship, employment and other demographic variables. These results suggest that in parts of the country with stricter deportation and detention policies, citizen-children in mixed status Mexican families are less likely to receive the social services for which they qualify.

Protection for mixed status families seems beyond reach as policies become more restrictive. A new executive order presented by the Trump administration further limits access to healthcare for Latinx citizen-children by threatening previously protected applicants with potential deportation or denial of citizenship application [24]. Perreira et al. described how the order would expand the definition of a "public charge" from someone who depends on government assistance for greater than half of personal income to include "any immigrant who 'uses one or more public benefits'" [25]. Enrollment in health and nutrition programs once excluded from consideration, even by citizen spouses and children, would then be considered in public charge determinations. With a possible Medicaid and Children's Health Insurance Program (CHIP) disenrollment rate between 15% and 35% if the measure is approved, approximately 875,000 to 2 million citizen-children with a noncitizen parent would lose coverage despite retaining eligibility [26]. Thus, programs designed to serve less fortunate citizens would become a black mark for mixed status families and further isolate them from the healthcare community.

The impact of losing access to services like Medicaid and CHIP for those who cannot afford private insurance is significant, as loss of healthcare coverage has long been a predictor of poor health. In 2002, the Institute of Medicine found that uninsured adults in the U.S. have less access to recommended care, receive poorer quality of care, and experience worse health outcomes than insured adults [27]. Systematic literature review also finds that having health insurance provides robust health benefits for adults suffering from chronic and acute conditions [28]. Though they are commonly thought to be healthier and therefore less needing

of insurance, children are similarly affected by loss of coverage. Uninsured children experience a delay in care when they develop a health problem and are at increased risk of missed diagnoses of serious problems. These undiagnosed and untreated conditions can have negative effects on functioning and quality of life [29]. Dafny & Gruber further showed that Medicaid expansions between 1983 and 1996 decreased avoidable hospitalizations among children by 22% [30]. Since the implementation of CHIP in 1997, there has been a 63% drop in the uninsured rate among U.S. children [31]. A significant decline in enrollment would therefore put more children at risk of delayed hospital care and loss of access to preventive medical care.

Clearly, the fear of forced removal directly affects the health of citizen-children whose caregivers may be at risk and indirectly impacts health by hindering citizen-children's ability to access the resources they need. This opposes the right conferred by Article 25, Section 1 of the UDHR, which reads, "Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including … medical care and necessary social services" [17]. A legitimate fear of deportation due to widespread punitive policies affects the entire Latinx community and consequently reduces their utilization of public health resources. Citizen-children are not enjoying the rights to which they are entitled according to the UDHR and may suffer greater risk of adverse health outcomes as a result. Through community-wide fear spurred by increasingly aggressive immigration policy, a large number of citizens are being denied the right to medical and social services they are guaranteed.

CONCLUSION AND RECOMMENDATIONS

The current situation created by immigration policy-makers places citizens in harm's way by generating community-wide fear through discriminatory policies. The right to freedom from discrimination has been violated by punitive measures that disproportionately affect the Latinx community. Legislation empowering state and local forces to act on behalf of federal immigration forces has driven a wedge between Latinxs, both documented and un-

Artist: Sebastian Voortman

documented, and the agencies that are meant to protect the citizenry. Objective measurements of deportation rates demonstrate targeting of Latinxs and the perception of immigration policy as discriminatory by the Latinx community mirrors this trend. The right to freedom from discrimination agreed upon in the UDHR has therefore not been respected.

Increased rates of deportation and detention result in crippling fear of enforcement agencies. This alienates citizen-children of mixed status families from the institutions that are meant to protect them and serve their needs. The stress of being identified by ICE or other government forces, even among authorized citizens, decreases enrollment in programs like Medicaid and hinders attendance at healthcare appointments. This is an infringement of the right to access medical care as guaranteed by the UDHR.

With both healthcare and immigration policy in upheaval under the Trump administration, protecting access to affordable medical care and social programs for citizen-children must become a top priority for all healthcare professionals. The medical community risks losing contact with a vulnerable patient population unless providers make a concerted effort to maintain hospitals and clinics as refuges for community members regardless of documentation status. In accordance with the Health Insurance Portability and Accountability Act (HIPAA), medical facilities must protect sensitive information and safeguard it from intrusive forces, including ICE, that attempt to turn clinics and hospitals into tools for tracking undocumented immigrants. It is also imperative to maintain trust by expanding outreach programs and Spanish language services to better serve a progressively isolated community.

Beyond clinic walls, medical associations and advocacy groups must lobby local, state, and federal legislative bodies to understand the far-reaching consequences of immigration policy. While undocumented adults may be the primary targets, a generation of citizen-children is suffering life-altering consequences. It is the responsibility of medical professionals to communicate the impact of detention and deportation on the public health of our citizens.

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VIEWPOINT
Health Policy

A Painful Reality: Unequal Access to Opioids in Developing Nations

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Vincent, a young medical assistant in rural Ghana, is called away from an interview with myself and other visiting research students to triage a new trauma patient. Minutes later, he returns and reveals to us that the patient was a 35-year-old man with end-stage cancer who was brought to the hospital following a suicide attempt, which was ultimately successful. "He couldn't tolerate the pain," Vincent explained. "The temptation to relieve his pain overcame him." Without access to adequate pain control, which we depend on in developed countries, this young man opted to end his own life as his only remedy.

While the global population continues to age, and with great advancements in the treatment of infectious disease, the burden of cancer and other chronic diseases is rapidly growing worldwide. In Western medicine, palliative care is a subspecialty focused on providing relief from the symptoms and stress of a serious illness. Palliative care services are readily available in developed countries, and these services play a crucial role in both end-of-life care and management of chronic suffering. However, in low-income countries, these professional services are few and far between, leaving millions to live with severe pain without hope for relief. Around two-thirds of patients with advanced cancer have pain. However, only about 6% of all specialty-trained palliative care services are located in Asia and Africa, where the majority of the world's population lives [1]. Similarly, the developing world only accounts for about 6% of the global morphine consumption, despite being home to almost 80% of the world's population [2]. In fact, more than 150 countries have no access to morphine [3]. Felecia Knaul, an international health economist and author of a groundbreaking 2017 Lancet publication on this topic, says the disparity in access to palliative pain control across the world is "one of the greatest, most ubiquitous, and at the same time most remediable inequities I've ever seen in any area of public health or social development" [4].

An inadequate supply of controlled and prescribed pain treatments has led many African countries to illicitly grow and use cannabis, which is the main drug of abuse, accounting for over 60% of drug treatment demand in the region [4]. Legalizing medicinal cannabis to address the pain treatment disparity is a highly debated topic, but it cannot currently serve as a suitable solution due to the unproven efficacy of cannabis against moderate to severe cancer pain. Increasing the availability of oral opioid formulations and professional palliative care services in these regions would not only reduce the illicit use of cannabis but would also provide a more effective and controlled alternative to treating pain.

High quality cancer treatment facilities and adequate training of cancer specialists may be unattainable in resource-poor areas due to the immense costs and demands for infrastructure. However, it has been shown that palliative care can be a cost-

effective public health entity. Morphine has traditionally been the pain treatment of choice in the developing world. Compared to other opioids and separate drug classes, such as anxiolytics and analgesics, morphine has appropriate strength for treating cancer pain while also having widespread availability, familiarity, and low cost. Quite simply, morphine is effective, easy to make, and amazingly cheap. Ten milligrams of generic morphine should only cost about 1 cent (U.S.) to produce, and a recent report determined that enough morphine to treat the entire world for end-of-life suffering would cost only $145 million a year. This is miniscule compared the to the $100 billion a year that the world's governments spend on enforcing the global prohibition of drug use" [4].

The low cost of morphine makes it the archetype of cost-effective pain relief medications for low- and middle-income countries. However, despite its low production cost, countries face an uneven playing field when it comes to paying for morphine, it has been found that drug companies preferentially supply more expensive opioids to low-income countries; drug companies are uninterested in selling generic morphine because it yields little profit [4]. The overall cost of essential medicines needed to deliver palliative care in Rwanda would cost the country three times more than if the nation had access to the lowest international prices. For injectable morphine alone, Rwanda pays nearly six times the lowest price [4]. The inaction of policymakers worldwide, who are likely influenced by the American opioid epidemic, are allowing big pharma to restrict affordable morphine to those who need it most. Allowing the pharmaceutical industry to restrict access of affordable pain medications to low-resource countries is, simply, an abuse of power. With increased awareness and advocacy, policymakers around the world could pass legislation forcing pharmaceutical companies to make oral immediate-

Artist: Leela Breitman

release, off-patent morphine more affordable in order to meet the worldwide demand.

It is clear that the ripples of the American opioid epidemic are being felt around the globe. Because of this epidemic, the word "opioid" has acquired a harshly negative subtext. Legislators and philanthropists in the developing world are now opposing the import of opioids out of fear that increasing availability will trigger another epidemic of addiction abroad. Meg O'Brien, founder of Treat the Pain, a group devoted to bringing palliative care to developing countries, believes this "opiophobia" is illogical. As she stated in a recent interview, "The U.S. also has an obesity epidemic, but no one is proposing that we withhold food aid from South Sudan" [5]. The most recent World Health Organization List of Essential Medicines includes 14 palliative care medications, including morphine and codeine [6]. Therefore, governments restricting opioid imports due to fear of an American-style epidemic is a marked overreaction that fundamentally denies its people medicines that are part of the "minimum medical needs for a basic healthcare system."

Uganda is a prime example of a nation that has implemented a successful model for innovative palliative care in Africa. Uganda's success in improving access to opioids has been facilitated by long-standing public-private partnerships between Uganda's government and private hospice organizations. These agreements have led to the allocation of specific funding for the purchase and local manufacturing of morphine. In addition, orally administered liquid morphine is now locally reconstituted and distributed, free of cost to the patient [7]. Diluting and packaging morphine in drinkable bottles prevents the possibility of intravenous administration, which inherently lowers the abuse potential while appropriately relieving pain. Importantly, this increased access to therapeutic opioids in Uganda without evidence of illicit diversion [9]. Perhaps as important as opioid availability is the broadening of opioid prescribers. This was achieved in Uganda in 2004 with a government-supported statute that permits nurses and clinical officers who have undergone specialized training to legally prescribe oral morphine for pain management [8]. As a result of the collective effort to increase opioid availability for palliative care, morphine consumption increased more than three-fold in Uganda between 2010 and 2014 [7].

The Ugandan model is one that can serve as a blueprint for other Sub-Saharan African countries to follow, but it is not a standalone fix. Despite the increase in availability, opioids are still largely unavailable at public health facilities, are unaffordable as a result of regulations from pharmaceutical companies that limit supply, and are associated with persistent negative attitudes and fear surrounding opioid prescribing [7].

Prevention is generally considered the keystone of public health ideology, but we cannot morally continue to ignore those who are already suffering. Philanthropists and well-intended clinicians cannot solve the problem on their own, and Uganda's success has demonstrated that improved palliative care is feasible even in resource-poor settings if there is adequate and prioritized government support. As long as policymakers continue to allow pharmaceutical companies to determine who can and cannot access affordable medications, the developing world will not stand a chance. While pain has neither a viral internet challenge to raise awareness nor a celebrity ambassador, layering pain treatment onto any evolving health care system—no matter the disease—is as vital and reachable a goal as any.

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REVIEW
Science

From Sepsis to Pepsis

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Septic shock is a formidable medical problem, with a mortality rate of greater than 20% and the dubious distinction of being the first among all causes of death in intensive care units [1]. Although we understand that septic shock is caused by systemic infection, the molecular mechanisms by which sepsis exerts its effects in totality, including in shock, remain obscure. Therefore, virtually all of the recent clinical trials aimed at reversing septic shock pharmacologically have been unsuccessful. Thus, septic shock remains a condition stubbornly resistant to the miracles of modern medicine, with a considerable risk of death and only supportive treatment available.

He who forgets the past is doomed to repeat it; thus so any discussion of sepsis must begin with a historical perspective on the condition. It was the Egyptians some 4,000 years ago who put forth our first written history of a sepsis-like phenomenon, postulating that a dangerous substance known as "ukhedu" lived in all of our guts and could, if not kept in check, migrate through our blood vessels and even stop our hearts [2]. To stave off this deadly disease, the Egyptians set aside three days each month to give themselves purges and enemas. The Greeks took up the Egyptian concept of ukhedu and generalized it into "sepsis," which referred to putrefaction and was closely associated with things smelling bad (rotting meat, the contents of the colon). Sepsis was in tight balance with a complementary concept, "pepsis," which was associated with things smelling good (a delicious pot roast, an aromatic lemon verbena soap).

Having conceptualized sepsis, I will not linger much longer on the historical basis of our modern day understanding. However, a few highlights are too good to ignore, including a 1718 sketch of the "animalcules" that were initially proposed to cause sepsis (**Figure 1**), a sketch of an early experiment to determine the method of transmission of these animalcules that involved the incubation of various animals in a sealed barrel with putrid material ("miasma") at its base (**Figure 2**), and this description of an 1872 study of the bloodborne transmission of putrid material: "Casimir Davaine [a French physician who also discovered anthrax] injected pu-

trid blood under the skin of a rabbit; it died in 40 hours. The blood from that rabbit killed the next

Figure 1. Concept drawing of an animalcule, *adapted from [2].*

rabbit, and so on for 25 rabbits; the lethal dose became progressively smaller" [2].

These highly sophisticated experiments eventually succeeded in showing that sepsis was caused by systemic infection, helped along the way by the discovery of "bacteria." Louis Pasteur and Robert Koch set forth the germ theory of disease circa 1860, and since then, our understanding of sepsis has slowly advanced. We have come to understand that the immune stimulation by infection and the resulting immune response play important roles in inciting sepsis. For example, it was demonstrated almost 40 years ago that adoptive transfer of bone marrow from mice injected with endotoxin (a.k.a. lipopolysaccharide, or LPS) into other mice was sufficient to kill the recipient animals [3]. Follow-up work identified particular cytokines—in particular IL-1, IL-6 and TNFα—that were responsible for mediating the host inflammatory response to LPS and that could be blocked to prevent septic shock in mice [4]. Indeed, sepsis has been cured many times over in mice using anti-cytokine and anti-endotoxin approaches.

However, translation of these discoveries into treatments for human patients has yielded mostly disappointing results, and several landmark studies have been published with shockingly negative results regarding anti-cytokine therapy in sepsis. One study examined 28-day mortality following administration of an anti-TNFα monoclonal antibody in patients with septic shock, and the investigators found no association between treatment and survival [5]. Another large study administered an IL-1 receptor antagonist (IL-1ra) in the setting of sepsis and again found no effect [6]. Additional studies have taken a different track, hypothesizing that giving an immunostimulatory cytokine, such as GM-CSF, might induce proliferation of the cells required to fight sepsis (i.e., macrophages). Those results (16.6% mortality with GM-CSF versus 17.6% without GM-CSF in a meta-analysis) have been resoundingly negative as well [7]. In totality, efforts to translate our developing understanding of sepsis has perplexed investigators and significantly dampened optimism for cytokine-related therapies for sepsis.

Importantly, however, the authors of the IL-1ra study also performed a subgroup analysis of mortality by infection type and showed that IL-1ra therapy may confer a survival benefit in certain Gram-negative infections. Although such an analysis was not pre-specified and their study was not powered to conduct such a subgroup analysis, this result offered the valuable suggestion that distinct infections may operate through distinct mechanisms of sepsis. Supporting this model, a monoclonal antibody against the lipid A domain of endotoxin was shown to be efficacious in Gram-negative

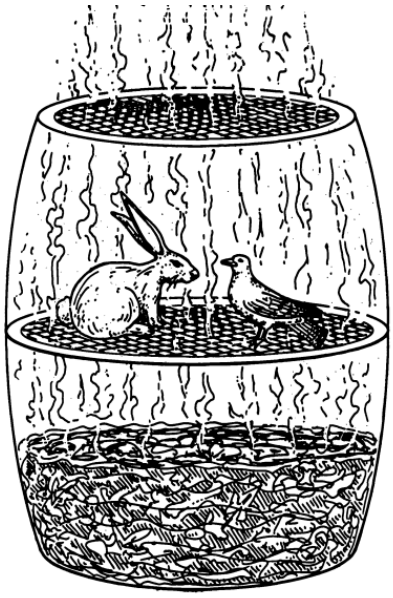

Figure 2. Animals incubating in miasma, *adapted from [2].*

bacteremia (37% mortality with the antibody versus 52% mortality without) [8]. The understanding of sepsis as a heterogeneous disease, defined uniquely by the particular infectious agent involved, has led to a new approach of addressing the problem of septic shock. While anti-IL-1, anti-TNFα, or anti-LPS drugs may be efficacious in the setting of particular pathogens, such as Gram-negative *E. coli*, they may be ineffective or even harmful in the setting of other infections, such as those caused by opportunistic *Candida* or Gram-positive *S. pneumoniae* (**Figure 3**).

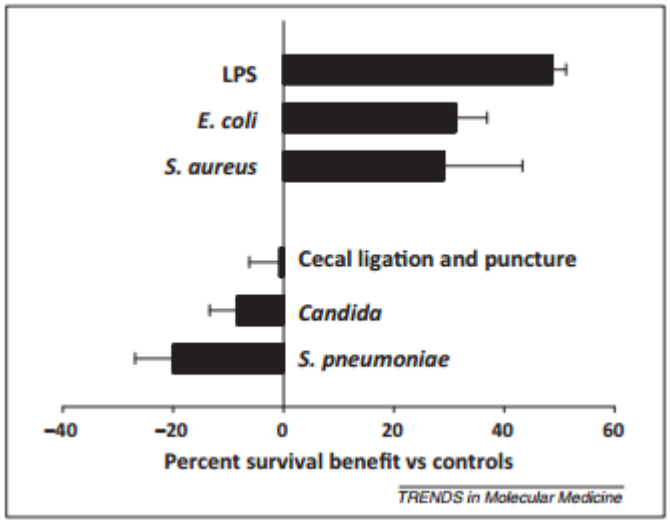

Figure 3. Meta-analysis of mortality in eight different preclinical models of sepsis following treatment with an anti-TNF antibody, *adapted from [12]*.

The challenge, then, is to unravel the molecular mechanisms of the immune response to particular pathogens and to systematically develop drugs that specifically target the molecular basis of sepsis. For example, in the case of LPS, recent immunological research has delved deeply into how LPS is sensed and how that signal is transduced into the production of pro-inflammatory cytokines. One important class of mediators is the inflammasome, a large oligomeric complex that forms in response to an innate immune stimulus. A series of recent studies in mice have demonstrated that LPS can activate a particular NOD-like receptor (NLR) inflammasome known as NLRP3, expressed in macrophages and dendritic cells, via an initial priming event and a successive, direct activation event [9]. NLRP3 then oligomerizes and cleaves a downstream activator, caspase-1, to produce an active protease that goes on to cleave IL-1β and IL-18 into their active forms. Importantly, caspase-1 also cleaves a protein called gasdermin D (GSDMD), which forms pores in the cell's plasma membrane and allows for release of the now-activated proinflammatory cytokines into the extracellular milieu [10]. These findings have rounded out our biological understanding of how inflammation results from infection—LPS stimulates NLRP3, stimulating caspase-1 cleavage, GSDMD production, and IL-1β/IL-18 release into the blood—thus allowing a more coherent understanding of the altered biological state in sepsis and identifying new targets for intervention (i.e., an NLRP3 oligomerization inhibitor if we want to turn down inflammation, or increased GSDMD production if we wish to turn it up). GSDMD activation has been shown to be effective in controlling both *E. coli* and *S. aureus* infection [10], both of which were also responsive to anti-TNF therapy in the setting of sepsis (**Figure 3**), offering a compelling link between the clinical picture of sepsis and our molecular understanding of infection and the immune response.

Altogether, our understanding of the NLRP3 inflammasome offers a compelling model for how we might approach infectious triggers of sepsis in general. One might expect, for example, that exploring other inflammasomes that have not been well characterized (there are 34 different genes coding NLR inflammasomes in the mouse genome) may hold the key to understanding how the immune system senses and responds to distinct infections. If we can identify the particular immune mediators produced in response to particular pathogens as well as the mechanistic basis for said production, we may very well be able to intervene rationally to inhibit or promote production of these mediators as appropriate, thereby effectively controlling sepsis.

This strategy does bring about unique complications. Future clinical trials investigating therapies for septic shock will need to stratify patients by infection type in order to generate appropriate data. To enable such a stratification, improved diagnostics must be developed to identify particular types of infections within a clinically actionable timeframe for septic shock, much in the same way that we culture microbes to understand which anti-

biotics may be efficacious for a given infection. A major key is the clinically actionable timeframe: targeted therapies for septic shock, an acutely deadly condition, will not work if there is a need to culture out infections for a week prior to initiating treatment. Additionally, many episodes of sepsis are not uncomplicated, monogenic infections but rather mixed infections with several different pathogenic organisms with which to contend. In such cases, the appropriate therapies may not be immediately evident, and additional research into more complex models will be necessary. Cecal ligation and puncture, a leading mouse model of sepsis where the mouse's cecum is closed off and punctured within the abdominal cavity to induce systemic infection [11], has so far proved resistant to cytokine therapies and poses a clear illustration of the challenges of complex infections (**Figure 3**).

Still, the first step towards solving these difficult problems is by answering the easier ones. Better definitions of the molecular stimuli, mechanisms, and mediators of inflammation in response to infection will be an important stride toward improving outcomes for patients with distinct and heterogeneous septic manifestations—helping to move patients, as the Greeks might say, from sepsis to pepsis.

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Bad Hearts and How Firefighting Will Come Back to Haunt Me

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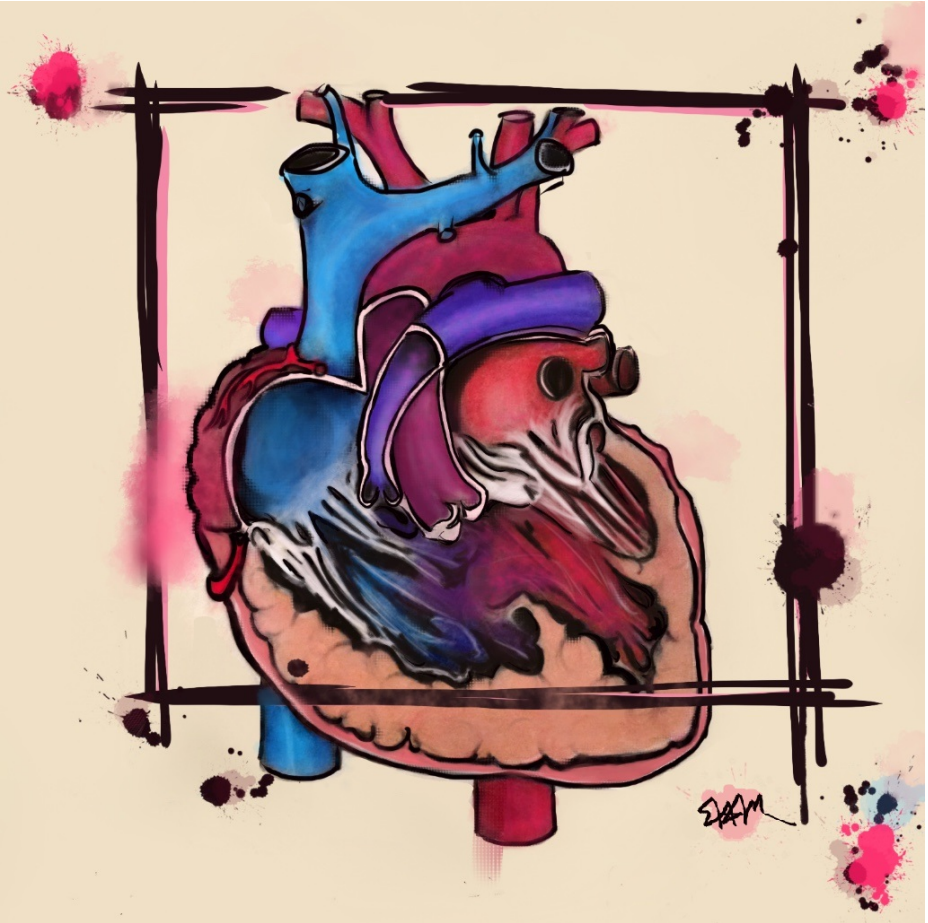
Firefighting has long been known as a dangerous profession. Most research investigations of the deaths of first responders focus on the traumatic line-of-duty deaths and the higher incidence of cancer later in life. However, nearly half of on-duty deaths actually have cardiovascular causes. While some of this can be attributed to increasing rates of obesity in the fire service, there are also large numbers of young, otherwise healthy firefighters dying of heart complications, as well as reports of unusual arrhythmias in older firefighters. This realization prompted further investigation into the effect of under-recognized cardiac stressors in this high-pressure profession.

I am one of those clichéd medical students who has wanted to be a doctor since childhood, and having finally made it to medical school is a dream come true. That being said, I will go to my grave insisting, as my father and so many others do, that firefighting is the best job in the world. The four years I spent getting up at 2:00 AM to the beeps of a loud pager, driving huge red trucks around town, and running into buildings everyone else was running out of were some of the most meaningful years of my life, having taught me a great deal about life, teamwork, and accountability. But each of those years came at a cost, and it may be decades before I know just how high that cost will be.

My father was a career firefighter for 13 years. While he also claims that those were the best years of his life, he has begun to see the health costs of firefighting. In the last few years, he has started to make regular trips to funerals, first for his chiefs, now for some of his officers, and soon for his crewmembers. He says some members of his old engine company envy him, as they can see their own clock ticking after a much longer firefighting career, and they think he got out in time. For older firefighters, attending funerals can almost become part of the job. While many people might imagine that these firefighters died from complications of cancer, it is not that simple.

Recently, my father has been considering a cardiac ablation procedure for recurrent premature ventricular contractions (PVCs). After his cardiologist ran a whole battery of tests uncover the root cause of the PVCs, he simply told my father that this is something cardiologists always seem to see with firefighters later in life. If these arrhythmias were to occur in most other people, a physician might push harder to address them, but with firefighters they are just another consequence of a job well done. My father and I have often traded stories and hearsay about what might be causing firefighters to have such problematic hearts later in life. People on the job have blamed the lack of sleep, the repeated hits of adrenaline, and the harsh wakeup produced by loud pagers—but those were all just theories. So, I decided to take a close look at the scientific literature for some hard answers. Unfor-



Artist: Elaina Murray, M.D.

tunately, while there is plenty of literature on cancer in firefighters, research on the effects of decades of adrenaline, stress, and interrupted sleep on the cardiac health of firefighters is scarce. What evidence does exist, however, is quite intriguing.

Cancer gets most of the attention in research on health complications in firefighters, but cardiovascular disease is what is really killing them. A CDC analysis from 2004 found that over 45% of on-duty firefighter deaths were caused by cardiovascular disease, and the proportion is not improving over time [1,2]. The majority of investigations into the cardiac health of firefighters have either focused on the chronic effects of obesity on cardiovascular health or the effects of acute firefighting stressors on cardiovascular health.

Obesity has well-documented impacts on cardiovascular health in the general population. It is associated with increased systemic inflammation, endothelial dysfunction, and resulting atherosclerosis, and it increases the risk of hypertension, heart attack, and stroke [3]. There has long been strong evidence of both immediate and long-term health benefits of weight loss [4]. The rising rates of obesity in the fire service could account for a large portion of cardiovascular-related deaths, but this does not explain why a large population of firefighters who are young, fit, and have not yet accumulated a substantial vessel disease burden, are also dying from cardiovascular events.

To understand what could contribute to the deaths of these young, fit firefighters, I looked into the cardiovascular consequences of vigorous exertion, like that required of those working on the fire scene. One study that analyzed high-level athletes showed that the risk of sudden cardiac death increases 2- to 3-fold during extreme physical exertion [5]. In line with this finding, firefighters are at

remarkably increased risk of death during physically stressful fire suppression activities (RR 22.1) [6]. In fact, the work during fire calls is strenuous enough to induce substantial clotting changes in firefighters even after 2 hours of recovery [7]. Both immediately after fire suppression activities and after 2 hours of recovery, firefighters had substantially increased platelet numbers, activity, and coagulation potential, along with a decreased partial thromboplastin time. Fibrinolysis was initially increased, but this increase was not maintained for as long as the increased clotting potential, which could help to explain some of the increased risk of cardiovascular death in the hours following strenuous emergency calls as their clotting systems fell out of balance.

The changes induced by physical stress, however, do not explain the increased cardiovascular risk associated with the many emergency calls that do not require strenuous physical activity. When considering other unusual aspects of firefighting that could explain this increased risk, long shifts and frequently interrupted sleep come to mind. One study found that firefighters who reported working sixteen 24-hour shifts in the last month had an average 5.0 mmHg higher diastolic blood pressure compared to those who reported working eight to eleven 24-hour shifts in the last month [8]. This raises the possibility that an intense firefighting schedule creates chronic stress on the cardiovascular system. Another study found that firefighters who were sleep deprived (getting 4 hours versus 8 hours of sleep) had significantly elevated cortisol levels, particularly in the afternoon and evening [9]. Given that getting 4 hours of sleep is the norm for firefighters, there is a need for more in-depth research into the effect of disrupted circadian rhythms, sleep deprivation, and increased cortisol levels on cardiac health in this population.

There are limited studies of the molecular regulation of circadian rhythms in humans, but an impressive molecular clock has been shown to drive circadian rhythms in mammals. This clock is driven by core-clock genes *Bmal1*, *Clock*, *Per1/2*, and *Cry1/2*. These genes work through a cyclic mechanism, whereby BMAL1 and CLOCK dimerize, activating PER and CRY. The accumulation of PER and CRY gene products then inhibits BMAL1:CLOCK activity [10]. This feedback loop is essential to regulating many clock-controlled genes. By immunoprecipitation analysis, the BMAL1:CLOCK complex binds at more than 2,000 sites across the genome in liver tissue [11]. Studies in mice have shown that knockouts of various molecular clock genes predispose mice to accelerated aging; increased cancer risk; hyperlipidemia and insulin insensitivity; and, in the case of *Bmal1* knockout mice, dilated cardiomyopathy. Disrupting circadian rhythms in skeletal muscle led to dysfunction in sarcomere arrangement and decreased force production, along with decreased mitochondrial volume and increased respiratory uncoupling [11]. The disruption of circadian rhythms also changed muscle fiber type, causing a notable shift towards oxidative fiber types and reduced glucose uptake. While these are mouse studies, it is interesting to consider the whether these impacts could also be present in humans as well, and in firefighters in particular. If the phenotypes are even remotely consistent, disrupted sleep patterns could be predisposing firefighters to diabetes and obesity, resulting in downstream cardiovascular problems. Additionally, skeletal muscle dysfunction and decreased force production could put firefighters at greater risk during strenuous physical activity.

Furthermore, there is evidence that the effects of disrupted circadian rhythms go far beyond skeletal muscle changes. As it turns out, the gut also has its own peripheral circadian clock. While this clock can operate independently of the central circadian clock, it is generally synchronized with the other molecular clocks in the body. The gut clock is primarily regulated by the time of eating (and firefighters love to eat after getting back from a call at 3:00 AM). One group found that environmental circadian rhythm disruption can cause intestinal microbiota dysbiosis in both mice and humans, particularly when combined with dietary stress like a high-fat diet or alcohol consumption [12]. The study found an increase in pro-inflammatory microbiota that put the host at risk for immune dysfunction. Another study transferred intestinal microbiota from jet-lagged and non-jet-lagged humans into germ-free mice and found that the mice with bacteria from jet-lagged humans developed obesity and

glucose intolerance not seen in the control mice [13]. While mouse studies may not translate perfectly to human physiology, these results raise interesting points. The dysrhythmic eating patterns of firefighters may predispose them to dysbiosis favoring pro-inflammatory microbes, thus making them more likely to experience metabolic syndrome. Thus, they would not only be predisposed to obesity and diabetes but also to systemic gut inflammation that increases the risk of developing atherosclerosis, further contributing to the high rate of cardiovascular disease.

While there are a number of ways in which disrupted circadian rhythms could indirectly impact the cardiovascular system, a direct impact is also possible. A study of the circadian rhythmicity of Kruppel-like factor 15 (Klf15), a protein associated with metabolism and cardiac hypertrophy in cardiac tissue, showed that the Klf15 gene is transcribed in a dose-dependent manner in response to the Bmal1/Clock complex [14]. In addition, the Klf15-dependent transcription of KChIP2 played a key role in rhythmic variation in cardiac ventricle repolarization and susceptibility to arrhythmias and sudden cardiac death. In another study, the molecular clock in cardiomyocytes was found to regulate the expression of Kcnh2, which encodes a potassium channel important for normal ventricular repolarization [15]. Additionally, disruption of the circadian clock led to an unmasking of long QTc intervals in the light phase that were not seen in normal mice. While speculative, this phenomenon suggests a novel factor that puts firefighters at an increased risk for cardiovascular disease. There are many LED lights involved in emergency responses, and evidence suggests that these lights are quite effective

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at confusing the normal light-dark cycle. If firefighters are already prone to arrhythmias due to disrupted circadian rhythms, being forced abruptly into an artificial light phase, coupled with the intense adrenaline stimulation associated with every call, could put them at a substantially elevated risk of arrhythmias. Taken together, these studies provide some concerning evidence that disruption of the molecular clock can lead to an increased risk of arrhythmias and sudden cardiac death. However, more investigation with human studies is needed.

Altogether, the significantly increased risk of death secondary to cardiovascular disease in the firefighter population has a multitude of potential causes, including several beyond the obvious. Obesity and chronic stress may play large roles, but emerging evidence also points to the hazard of disrupted sleep cycles. There is increasing evidence that disrupting the finely tuned central and peripheral circadian clocks could create a host of problems, including gut dysbiosis, metabolic dysfunction, arrhythmias, and sudden cardiac death. While more evidence and studies in humans are needed, the emerging risks of disrupting circadian rhythms highlights the importance of studying lesser-recognized contributors to cardiovascular disease. Evidence is starting to surface about the long-term consequences of a career in firefighting, but we still have a limited understanding of the impact that daily firefighting activities have on the body.

We all love things that are bad for us—be it chocolate or Netflix binging. For me, that includes firefighting. The fried station food, the sleepless nights, the gear coated in carcinogens—none of it was good for me. If I were to take the literature at face value, I might sleep easy knowing I had left those things behind, but I have now traded sleepless nights at the station for sleepless nights on the wards, which, we are starting to understand, might be just as dangerous as the dirty bunker gear full of cancer. That being said, if a paper comes out tomorrow showing absolute proof of the relationship between disrupted circadian rhythms, arrhythmias, and disrupted metabolism, you will still find me running around the ER at 2:00 AM. Sometimes the bad is worth it, but that should not limit us from delving into ways to improve the risks.

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HMSR

REVIEW
Science

Mitochondrial Dysfunction in Parkinson's Disease

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Parkinson's disease (PD) is a common, progressive neurodegenerative disorder characterized by the selective death of dopaminergic neurons in a small region of the brain called the substantia nigra. The death of these cells results in a number of debilitating motor symptoms, including a distinctive tremor, bradykinesia, and joint rigidity. One of the enduring mysteries of PD is the cause of death of dopaminergic neurons. Many different mechanisms have been proposed, including oxidative stress, mitochondrial dysfunction, proteasome dysfunction, and inappropriate immune activation. However, the late diagnosis of PD makes it hard to separate cause from effect. This paper describes several mechanisms related to mitochondrial dynamics that have been suggested by neurobiology, metabolism, and immunology researchers. Following a brief introduction of the key players—the proteins α-synuclein, Pink1, and parkin—this paper explores the emerging relationships between PD and the mitochondrial autophagy and antigen presentation pathways.

In the brains of Parkinson's disease (PD) patients, the protein α-synuclein forms neuronal aggregates, called "Lewy bodies," that have been linked to disease pathogenesis [1]. Although α-synuclein is predominately cytosolic, the fraction that is associated with mitochondrial membranes is increased in PD [2]. Furthermore, there appears to be a bidirectional association between α-synuclein accumulation and the function of the mitochondrial electron transport chain. Chemical inhibition of mitochondrial Complex I results in α-synuclein accumulation and development of Parkinson's-like symptoms in both mice and humans [3]. A profound example of the neurological effects of disrupting mitochondrial activity is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) a mitochondrial poison that is a contaminant of improperly produced synthetic heroin and produces permanent parkinsonism [4]. Conversely, α-synuclein accumulation has been shown to impair mitochondrial function by inhibiting TOM20, an essential subunit for the mitochondrial import of cytosolically-produced proteins [5]. Taken together, these mechanisms suggest that α-synuclein and mitochondrial dysfunction may be linked in Parkinson's disease.

Several related mitochondrial pathways have also been implicated in the function of the proteins Pink1 and parkin, which are two proteins mutated in rare, hereditary forms of PD. Pink1 is a kinase targeted to the outer mitochondrial membrane (OMM), but it is usually rapidly removed by other proteins on the membrane. If Pink1 remains, it phosphorylates and activates the ubiquitin E3 ligase parkin, which marks the mitochondrion for lysosomal autophagy ("mitophagy"). Extreme mitochondrial stress may cause the collapse of the proton gradient ("mitochondrial depolarization"), inhibiting normal protein import from the cytosol. Pink1

is left on the OMM, allowing it to trigger mitophagy [6]. These later steps have not been well studied, but there is emerging evidence suggesting that autophagy may be dysregulated in PD. If key autophagy proteins are knocked out (such as Atg5 and Atg7), mice develop progressive motor and behavioral deficits and begin to accumulate unspecified protein inclusion bodies [7,8]. Of note, Pink1 and parkin are also involved in mitochondrial fission/fusion dynamics, which are believed to be important for mitochondrial repair [6,9]. This represents yet another way in which the mitochondrial stress response may be suppressed in PD.

These fascinating results are consistent with many potential models. One possibility is as follows:

1. α-synuclein dynamics are disrupted in the substantia nigra. Multiple cells may be affected, or the defect may be transferred between neurons by a prion-like mechanism.
2. α-synuclein misfolding inhibits Tom20, disrupting mitochondrial protein import.
3. Mitochondria start to break down internally, causing them to depolarize.
4. Pink1 accumulates on the OMM, activating parkin and leading to mitophagy.
5. If enough mitochondria are damaged, the neuron may die.
6. Ongoing neuronal death results in the progressive symptoms of PD.

Recent research on the immune response to mitochondrial antigens suggests an alternative to steps 4-6 outlined above. In 2012, Soubannier et al. reported a novel pathway by which small "mitochondria-derived vesicles" (MDVs) are produced and targeted to lysosomes via an autophagy-independent mechanism [10]. In a later paper, the authors showed that the MDV pathway is responsible for mitochondrial antigen presentation in primary biliary cirrhosis, a rare autoimmune disease in which the immune system becomes sensitized to the mitochondrial protein α-ketoglutarate dehydrogenase. Furthermore, this pathway is inhibited by both Pink1 and parkin [11]. This suggests that in the context of cellular stress, dysregulation of Pink1 and parkin might favor the production of MDV's over mitophagy, increasing mitochondrial antigen presentation. Therefore, the mechanism of dopaminergic cell death may be immune attack, rather than direct mitochondrial damage. In this light, PD itself may be an autoimmune response to mitochondrial proteins. Although this is a bold idea,

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many recent papers have also suggested that inappropriate immune activation may be involved in PD pathogenesis [12].

The study by Matheoud *et al.* 2016 raises a basic question that remains unanswered [11]: why have humans evolved an elaborate mechanism to present mitochondrial proteins to the immune system? Three possibilities include the following:

(a) The pathway may have evolved to combat intracellular pathogens, but mitochondria still resemble their bacterial ancestors enough to be mistaken for a pathogen.
(b) The pathway may be important for self-tolerance.
(c) The immune system may help destroy cells that have a large number of slightly damaged mitochondria.

Current literature makes certain possibilities more or less likely. First, Pink1 and parkin are indeed associated with protection against intracellular pathogens. However, this process is dependent up-

on classical autophagy proteins like Atg5, rather than the mitochondria-derived vesicle pathway. This makes option (a) less likely [13]. Similarly, mitochondrial proteins are included in a self-tolerance pathway involving thymic medullary epithelial cells (TMECs) and the autoimmune regulator "Aire," but this pathway is also dependent upon the autophagy pathway via Atg5 [14]. Option (b) could still be true if another mechanism of self-tolerance were involved, perhaps involving the peripheral immune system. Finally, the option of deliberate immune targeting could explain the observed immune response in PD, but this has not been directly studied on its own. If a study were to find that immune infiltration of tumors correlates with mitochondrial dysfunction, this would strengthen the likelihood of option (c).

Though the mechanisms of Parkinson's disease remain uncertain, it seems very likely that mitochondria and mitochondrial proteins play an important role in disease pathogenesis. The research described here suggests the intriguing possibility that changes in the mitochondrial stress response may alter the balance between mitochondrial destruction and repair, potentially recruiting immune cells in a larger systemic response. Changes in α-synuclein, Pink1, parkin, Tom20, and mitochondria-derived vesicles may trigger this shift, or they may become dysregulated later in disease pathogenesis. Either way, this research brings to light a novel modality for targeting PD and invites important and collaborative projects between neurobiology, immunology, and metabolism researchers.

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Using 2D Gait Motion Analysis to Evaluate the Mercer Universal Prosthetic Device in a Vietnamese Population

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Utilizing a "Universal Socket Design" with ultra-high molecular weight polyethylene material, the novel Mercer Universal Prosthetic (MUP) aims to provide an individual, adjustable, and comfortable option for low-income Vietnamese patients. Thus far, there have been no clinical trials or studies on the functional aspects of the device. The following article assesses the functionality of the prosthesis while serving as a stimulus for further research, such that design and functionality improvements can continue to be made. The study was conducted in three rural Vietnamese clinics, with 57 participants. The effectiveness of the MUP was compared to the patient's original prosthetic (Old P) in terms of gait mechanics using PRO.Vision 2D software. Specifically, total knee and hip angle range of motion (ROM), percentage stance phase and swing phases, and individual knee and hip angle ROM for each phase of the gait cycle were assessed and compared. No significant differences regarding overall percentage stance or swing phase, knee angle ROM, or hip angle ROM were found between the prosthetic types. However, certain individual phases of the gait cycle showed significant increases in knee and hip angle ROM with the MUP as compared to the Old P, possibly attributable to the lightweight property of the MUP. Ultimately, no overall difference was found between the gait mechanics of the Old P and the MUP. This suggests the MUP as an affordable, cost-effective prosthetic alternative.

Introduction

The Mercer on Mission Vietnam Orthopedic and Prosthetic Clinic Program is a Clinton Global Initiative recognized non-governmental organization (NGO) that aims to improve the lives of underprivileged Vietnamese amputees who are exposed to landmines and other forms of trauma in Vietnam. The patients are fit with devices at no cost to them during a 4-week summer program. The program relies on Mercer Universal transtibial prostheses and transfemoral prostheses, which cost approximately $100 (USD) and $150, respectively. In comparison, the cost of custom-designed transtibial prosthetics in the United States ranges from $4,000 to $10,000 [1].

In the developing world, there is an increased need for affordable yet functional prosthetic devices. For example, surveys in India revealed that patients prefer to buy devices less than INR 20,000 (roughly $287.00), which are widely unavailable [2]. Novel prosthetic designs have been created to address such needs of underserved populations around the globe. For example, an upper-limb prosthesis has been developed for $20.66, made using a socket

composed of Piacava, a renewable resource made from tree bark [3]. In another case, a prosthetic knee prototype design using an early stance lock and a friction damping system has been developed to allow full functional capabilities at both a low metabolic and monetary cost [4]. Additionally, 3D-printed transradial devices estimated to cost around $300 are under development [5]. Furthermore, currently available SATHI transtibial prosthetic devices using polypropylene material cost around $85, providing a light-weight option for many patients [6]. The device studied here, the Mercer Universal Prosthetic (MUP), was originally created to address a specific need amongst underprivileged amputees in rural Vietnam; however, like the aforementioned devices, its ultimate goal is to function as a cost-effective prosthetic that provides a natural fit and mimics the amputee's natural gait.

Mercer Universal Prosthetic Design

In general, amputees have been shown to prefer a prosthetic socket that is malleable to residual limb changes, heat, and activity while providing comfort [7]. The Universal socket design of the MUP intends to accommodate a variety of residual limbs, permitting volunteer fitters to individually fit patients (**Figure 1**). Moreover, the MUP socket design strives to be flexible enough to modulate for a patient's needs over time [8].

Figure 1. Mercer Universal Prosthetic. Transfemoral (right) and transtibial designs (left).

Keeping such design goals in mind, pre-sized manufactured Mercer Universal sockets are constructed from lightweight, ultra-high molecular weight polyethylene (UHMWPE), a material that has been used in devices such as the Jaipur HDPE prosthesis [6,8]. Prosthetics using lighter weight materials have been associated with enhanced gait mechanics, decreased fatigue, and improved physiological energy expenditure in the ambulating patient [9]. UHMWPE allows for socket adjustability—that is, after different length and diameter molds are manufactured for a certain number of socket sizes, a "V-cut" is created along the lateral side of the socket, spanning two-thirds of the socket length [1,8]. This "V-cut" design allows the socket to change circumferential sizes beyond the pre-sized manufactured sockets at any point in time [8]. Thus, as muscle atrophy may ensue in the patient's residual limb due to non-use, this compressive design aims to promote vascular flow to the residual limb, offsetting possible atrophic effects [1].

Additionally, the Mercer Universal Prosthetic uses a "patellar-bearing design" modeled after the "total-surface bearing design" used in other commercially available products in the West [1]. The patellar-bearing design has frequently been utilized in developing countries, including within the International Committee of the Red Cross prosthetic centers [10]. Unlike the "total-surface bearing design" that is modeled to distribute force equally on the residual limb and reduce pressure on normally pressure-sensitive areas, the "patellar-bearing design" allows pressure to be taken at the patellar tendon, whereby the pressure sensitive distal end of the residual limb is suspended from the bottom and bears no weight [1]. This design intends to be more practical than a total-surface bearing design, which requires frequent follow-ups and subsequent modifications for patients with varying residual limb sizes [1]. Such modifications may lead to a nonfunctional design whereby the forces are no longer evenly distributed but are localized to a pressure sensitive area, leads to pain, pressure ulcers, and sores [1]. In conclusion, the MUP utilizes lightweight material, a "V-cut" design, and a patellar-bearing socket, creating a design that may have improved functional outcomes compared to other de-

vices. Thus far, there have been no studies of the functional performance of the MUP device. Here, we used gait analysis to assess the quality and efficacy of the MUP.

The Gait Cycle

Gait analysis is a quantitative method conducted by specialists to test for pathological prosthetic gait and remedy any complications present in the device that may lead to functional gait disturbances [11]. Angle parameters at the hip, knee, and ankle joints are assessed during gait analysis. The gait cycle of each limb consists of two phases: the swing phase and stance phase. The stance phase is characterized by the following periods: heel strike, loading response, midstance, terminal stance, and pre-swing. Heel strike is the initial contact one heel creates with the ground. When the sole of the foot meets the ground, the weight of the body is shifted onto that limb, characterizing the loading response. The tibia sequentially rotates over the stationary foot in the direction of locomotion, marking the beginning of the midstance phase [12]. The onset of terminal stance occurs once the weight from the hind and midfoot regions transfers to regions of the forefoot. Next, in pre-swing, the weight from the limb transfers to the contralateral limb [12]. The swing phase is characterized by the following periods: initial swing, midswing, and terminal swing. Initial swing occurs from toe-off up until the limb is directly opposite the contralateral limb. Midswing follows until the tibia of the limb is vertically oriented [12]. Finally, terminal swing follows until heel-strike for the next stride occurs, and the cycle continues.

METHODS

This study was approved by the Institutional Review Board (IRB) and Office of Research Compliance at Mercer University in Macon, Georgia on August 22, 2016 (NHMC #H0606821).

Setting

721 patients from rural areas in Vietnam were fitted with Mercer Universal transfemoral and transtibial prostheses over a 4-week period during the summer of 2017 via the Mercer on Mission program, at no cost to the patients. The fittings took place at one of three clinics set up in the cities of Bến Tre, Bình Phước, and Thái Nguyên. Each clinic consisted of a prosthetic fitting center and a gait analysis center.

Participants

57 of the 721 patients met our study's inclusion criteria, as reported in **Table 1**.

Table 1. Study parameters.

Subjective Parameters	Objective Parameters
No weakness or difficulty during standing	Demographic: 20- to 60-year-old males
No weakness or difficulty during ambulation	Amputation: Transtibial amputation
Alert and oriented to place, time, and situation	Range of Motion score: 4/5–5/5
	Muscular Strength score: 4/5–5/5
	No past medical history of neuropathies, muscular pathology, degenerative disease, respiratory disease, cardiovascular disease, or recent surgeries

Procedure and Protocol

A space within the clinic was reserved for gait motion analysis. A treadmill was placed against a blank wall to prevent noise disturbance from the computer software, and two cameras were placed at the sagittal planes of the treadmill. After fitting, patients were encouraged to accustom themselves to the prosthetic within the clinic for at least 15 minutes. The protocol was fully described to the patient, and informed consent was verbally obtained.

Two-dimensional (2D) gait was analyzed in two planes: sagittal left and sagittal right. A colored LED sensor was placed to assess the sagittal plane of movement at five joints: the knee joint (below posterior convexity of the lateral femoral epicondyle), head of the fifth metatarsal joint, ankle joint (beneath the ankle on a horizontal line to the forefoot marker), shoulder (acromion), and hip (trochanter major). Sagittal Left sensors were placed on the left sagittal plane of the body, while Sagittal Right sensors were placed on the right sagittal plane of the body (**Figure 2**). Each plane was recorded so that both the natural and prosthetic limb could be assessed during ambulation with their old prosthetic

Figure 2. Gait Motion Analysis Sensor Placement. Left: Sagittal Left. Right: Sagittal Right.

and MUP prosthetic devices. Each patient's old prosthetic device was vastly different and non-homogenous. Each patient was required to be barefooted and wear fitted clothing for accurate sensor placement. For each patient, the protocol was repeated twice: initially beginning with their own personal prosthetic, and later with their newly fitted MUP. The warm-up time before each recording was neither recorded nor standardized; that is, the patient was recorded with each the device once they felt comfortable enough to walk. The patient was requested to walk on the treadmill using their normal ambulatory ground speed. In conjunction with the patient's feedback, the examiner set a comfortable walking speed for the patient. This speed remained constant for each plane (sagittal left and sagittal right) and device (MUP and Old P).

Once the patient was comfortable walking on the treadmill, the examiner would start recording using the PRO.Vision software. Cameras sensed the different movements and colors and transmitted the information to the software on the computer. The real-time gait motion analysis system generated a 2D composite of the patient during running or walking. Each recording lasted three gait cycles.

Analysis

The PRO.Vision software allowed complete assessment of gait motion and comparison of gait to a healthy reference population. The measurements were created using the software, where the examiner identified each phase of the gait cycle on the recorded video. The software system captured the LED lights to produce various measurements during the length of one gait cycle. Each patient was recorded three times; a PDF report was obtained on each recording and subsequently averaged to produce the overall score (**Figure 3**). Upon analysis, only 34 reports out of the 57 reports were studied due to technical disturbances with the camera recording or the PRO.Vision software.

After creation of the PDF reports, two angular parameters, hip angle and knee angle, were specifically assessed per patient. The ankle angle was not included in this analysis, as many patients' old prosthetic devices did not contain a foot device; therefore, we were unable to include any meaningful differences in our analysis.

The following parameters for the patient sample (n = 34) were averaged: percentage (%) spent in stance phase, percentage (%) spent in swing phase, overall knee ROM (◦), overall hip ROM (◦), individual knee ROM for each phase of the gait cycle, and individual hip ROM for each phase of the gait cycle (◦).

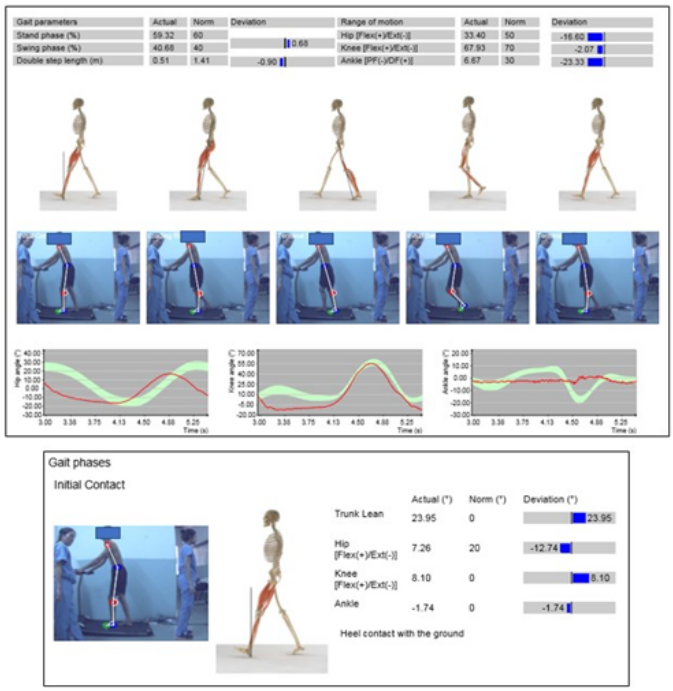

Figure 3. Example report produced by PRO.Vision.

Each of these parameters was compared between 2 different sets of groups: (1) the old prosthetic-wearing natural limb (Old Natural) and the MUP-wearing natural limb (MUP Natural) and (2) the old-prosthetic limb and the MUP prosthetic limb. Comparisons and sequential statistical testing were completed to assess for any meaningful differences in gait parameters between the MUP and Old P on either the prosthetic and/or natural limbs. Since the range of Old P devices from the patient sample population was vastly non-homogenous, statistical testing using a paired sample t-test was used to assess the data.

RESULTS

No statistically significant differences were found between the mean percentage patients spent in the stance and swing phase between the Old P and MUP, or between the natural limb with the old prosthetic (Old Natural) or natural limb with the MUP (MUP natural) (**Table 2**).

Table 2. Gait comparison. Shows average % time patients spent in stance phase or swing phase and overall patient hip and knee ROM during one gait cycle.

	Old P	MUP	Old Natural	MUP Natural
% in Stance Phase *Mean (SD)*	73 (4)	74 (3)	75 (4)	75 (4)
% in Swing Phase *Mean (SD)*	27 (4)	26 (3)	25 (5)	24 (5)
Hip ROM (◦) *Mean (SD)*	35 (8)	36 (7)	29 (7)	30 (7)
Knee ROM (◦) *Mean (SD)*	56 (14)	56 (10)	47 (6)	48 (7)

Additionally, no statistically significant differences were evident between mean total ROMs at the knee between the Old P and MUP, or the old natural and MUP natural (**Table 2**). A significant difference in the mean total ROM at the hip was found between the MUP natural and Old natural ($p = 0.031$), while no significant differences were found between the Old P and MUP at the hip.

Average angles at the knee joint were plotted over the eight phases of the gait cycle (**Figure 4**).

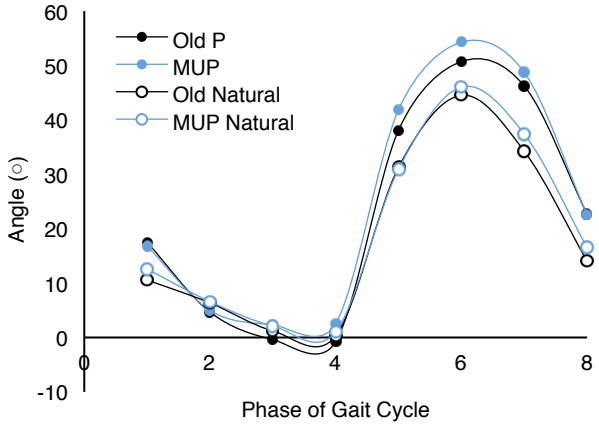

Figure 4. Average knee angles during one gait cycle. Depicts four different parameters (Old P, MUP, Old Natural, MUP Natural) over each phase of one gait cycle (1–8). 1: initial contact; 2: loading response, 3: mid-stance, 4: terminal-stance, 5: pre-swing, 6: initial swing, 7: mid-swing, 8: terminal swing.

With respect to knee angles, statistically significant differences were found between the Old P and MUP in phases 3 (mid-stance) ($p = 0.027$), 4 (terminal-stance) ($p = 0.008$), and 6 (initial swing) ($p = 0.045$) of the gait cycle, while such a difference was only evident in phase 7 (mid-swing) ($p = 0.042$) between the Old Natural and MUP Natural groups (**Table 2**).

Next, average angles at the hip joint were plotted over the eight phases of the gait cycle (**Figure 5**). The same four parameters were assessed and

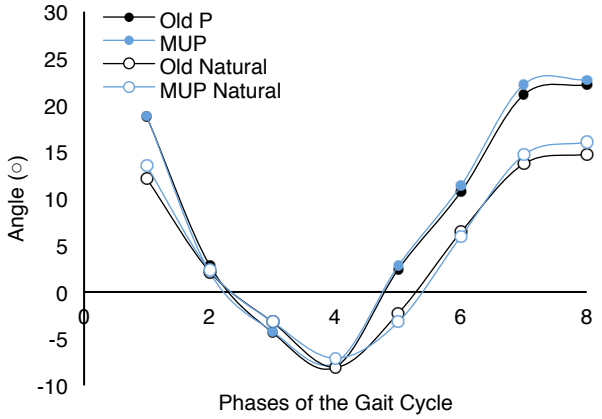

Figure 5. Average hip angles during one gait cycle. Depicts four different parameters (Old P, MUP, Old Natural, MUP Natural) over each phase of one gait cycle (1–8). 1: initial contact; 2: loading response, 3: mid-stance, 4: terminal-stance, 5: pre-swing, 6: initial swing, 7: mid-swing, 8: terminal swing.

compared. Statistically significant differences were found in average angles between the Old P and MUP groups in phases 1 (initial contact) ($p \leq 0.001$), 5 (pre-swing) ($p = 0.003$), 6 (initial swing) ($p = 0.003$), 7 (mid-swing) ($p \leq 0.001$), and 8 (terminal swing) ($p \leq 0.001$). The results were similar with respect to the old natural limb and MUP natural limb groups, where statistically significant differences were evident in phases 1 (initial contact), 5 (pre-swing), 6 (initial swing), 7 (mid-swing), and 8 (terminal swing) ($p \leq 0.001$ for all).

DISCUSSION

In Vietnam, the commercial cost of prosthetic devices is often prohibitively high. Here, we tested the effectiveness of a cost-effective alternative, the Mercer Universal Prosthetic (MUP), by conducting gait analysis. We found that MUP devices functioned similarly to existing devices; that is, we found no statistically differences with respect to mean % spent in swing phase and mean % spent in stance phase or total hip and total knee angle ROM for both prostheses. Therefore, the MUP does not alter the patient's gait drastically and provides the patient with a similar gait pattern that they are already used to. By enabling a similar overall gait pattern, the MUP provides an easy transition from wearing the Old P, as the patient is better accustomed to a device which mimics the overall functionality of their old prosthetic.

Hence, the MUP functions at least at the minimal standards set in place by the patient's older prosthetic. In fact, in some areas the MUP may function better. When specifically evaluating average knee angle ROM during each phase of the gait cycle, a statistically significant difference between the MUP and Old P in mid-stance, terminal stance, and initial swing phases was calculated. The MUP device achieved greater knee angle ROM at these phases compared to the Old P. We attribute the increased knee angle ROM of the MUP to be due to the MUP's lightweight polyethylene material (average weight: 1.23 ± 0.3 kg). The increased knee ROM provided by MUP provides greater movement during the last stages of the stance and initial stages of the swing phase. Additionally, a statistically significant difference between knee angle ROM of the Old Natural limb and MUP natural limb was found in mid-swing. We similarly attribute this increase in ROM to the lightweight material of the MUP.

When specifically evaluating the average hip angle ROM during each phase of the gait cycle, a statistically significant difference between the MUP and Old P as well as the Old Natural limb and MUP natural limb was calculated during initial contact, pre-swing, initial swing, mid-swing, and terminal swing. The MUP device could achieve greater hip angle ROM at these three phases compared to the Old P. Additionally, a statistically significant difference between the total hip ROM in the Old Natural limb and MUP natural limb was found. We attribute both the increased hip angle ROM of the MUP at the specific phases and the increased total hip ROM in the natural limb to the MUP's lightweight material. The swing phase at the hip is particularly inferred to be influenced by the polyethylene material, providing the patient with an improved ROM during individual phases.

The small sample size ($n = 34$) is a limitation of this study; in follow-up studies, we hope to increase the sample size to provide a larger representation of patient's older prosthetic devices while comparing them to the MUP. Additionally, a brief time interval was designated between fitting the prosthetic and beginning the gait study, possibly preventing patients from becoming adequately accustomed to the MUP during the analysis. In future studies, a longer time interval will be designated to allow the patient adequate time to become accustomed to the MUP, and the warm-up time between each recording will be standardized. Additionally, the design and functional characteristics (weight, material, cost, socket design) of the patient's Old P will be recorded to better categorize similarities and differences between the Old P and MUP devices. Further assessments including the patients' self-reported assessment of their comfort level, ROM and overall movement, and likelihood of adoption or continuation will be conducted.

In summary, the MUP provides a similar overall gait pattern compared to other prosthetic devices available in Vietnam. In some areas of the gait cycle, the MUP may provide improved gait function. Although there were no statistically significant differ-

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ences between overall hip and knee angle ROM, individual differences within individual gait cycle phases demonstrated the potential for the MUP to provide a greater ROM compared to other devices. This study was the first clinical research investigation of the MUP device, and we aim to continue further work to modify the device and its functionality to reach our goal of improving the lives of underprivileged amputees around the globe.

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Artist: Sandy Jiang

Bridging Academia and Industry in Healthcare: An Interview with Dr. Michael Rosenblatt

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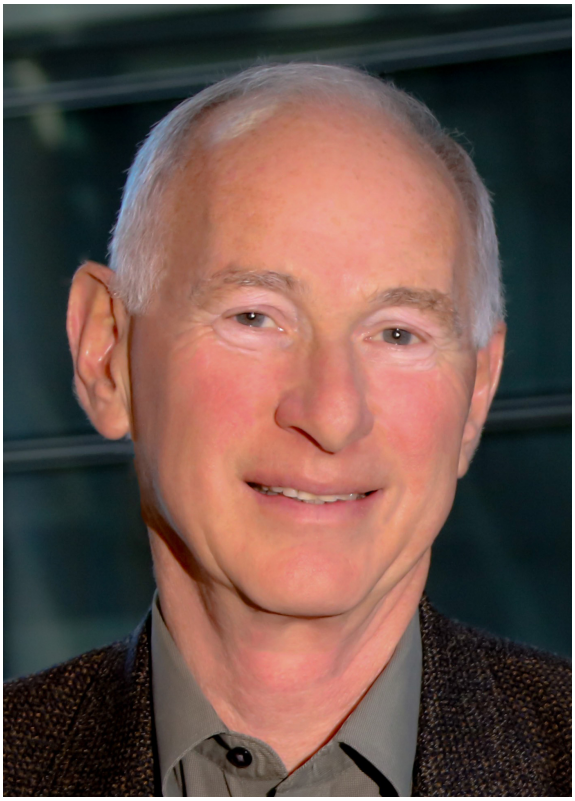
Michael Rosenblatt, M.D., is the Chief Medical Officer at Flagship Pioneering, where he leads global clinical development and medical affairs. Dr. Rosenblatt previously served as Executive Vice President and Chief Medical Officer at Merck from 2009 to 2016. He has had a distinguished career, with prior appointments as Dean of Tufts University School of Medicine; Robert H. Ebert Professor of Molecular Medicine and George R. Minot Professor of Medicine at Harvard Medical School; President, Harvard Faculty Dean, and Senior Vice President for Academic Programs of Beth Israel Deaconess Medical Center; and Director of the Harvard-MIT Division of Health Sciences and Technology. He holds 19 patents and has authored over 180 peer-reviewed papers and commentaries.



Nishu Uppal (NU): In medical school, we have been learning that figuring out how we can create value in health care outside of daily clinical practice involves choosing a path (i.e., choosing an area of research, pursuing another degree, etc.) early on in training. While we were trying to learn more about your background before today, we noticed that you have pivoted between several sectors, including clinical practice and academia as well the pharmaceutical industry. To start off, we'd like to hear more about your journey since completing your clinical training and about how you have evaluated new opportunities as you've made some of those career decisions.

Michael Rosenblatt (MR): Getting good clinical training is very helpful preparation no matter what you choose to pursue with your MD degree. It's applicable in almost everything, including research, policy, and administration, because it teaches a way of thinking and understanding what problems need to be solved.

MR: I never planned much of my own career, so I wouldn't advise people to sit down and plan it because who knows what you'll be interested in a few years from now. People change and fields change, so be careful not to over-plan. I'm an endocrinologist, which means I'm interested in receptors. Once you go through your training, it's important to keep displaying your receptors, see what binds to them, and understand what activates and interests you. I think that's the best career advice that I can give. If you keep an open mind, you will have insight and can be sensitive to what actually interests and motivates you based on your own experience, not on the advice or biases that others hold about certain areas.

When I was in medical school, I thought that I would have a career exclusively in academic medicine. I love academic medicine, and I spent half of my career in that. But early on in my career I had an opportunity to go to industry, and rather than rejecting it outright, as a number of people advised me to do, I saw the opportunity differently. Once I made that first decision to deviate from a prescribed career path, I became open to options that I would have dismissed outright in the past. That allowed me to evaluate each subsequent opportunity on its own terms, and I wound up making a number of career changes over the course of time.

NU: Your emphasis on remaining open-minded during training echoes sentiments expressed by other faculty who ventured outside of academia or clinical medicine. Were there aspects of the first opportunity in industry that seemed particularly compelling or interesting to you?

MR: Firstly, I consider clinical practice to be very rewarding, and I've tried to keep a frontline connection to patients throughout most of my career. However, opportunities in industry and elsewhere can offer the chance to influence healthcare and even transform disease for many more people than you can do by seeing patients one-by-one in your office. If you're involved in inventing an important drug and bringing it from the laboratory to clinical practice, you can have an impact on a tremendous number of patients. That's a different kind of way of approaching health for people. Since I really like basic science, especially the science that's fundamental to medicine, I came to believe that translation into products that can be clinically applied is really only possible from an industry platform. Academia generates many of the fundamental insights that industry relies on. However, it's rare that an academic can take a discovery and go all the way to something that other doctors are actually able to prescribe. That's what you do in industry, and that's what really captured my imagination.

On a personal level, I learned firsthand from my mother about the kinds of challenges that one has in an industry. My dad died early when I was just a kid, and my mother took over his business. At the dinner table, she would discuss with my sister and me the challenges she faced. Since I found them interesting and I didn't share the biases that many of my colleagues held about industry, it helped me make that first leap into industry. In short, I would say it was science that captured my imagination and that I wasn't hindered by a set of biases that precluded my trying industry out.

NU: It sounds like you're illustrating the dichotomy between the groundedness that one can find at a patient-facing level in the clinic and the ability to scale one's efforts by going into industry. Do you think that your current position at Flagship Pioneering is another opportunity for you to scale your own efforts and seek ways to transform healthcare?

MR: Flagship is a venture firm that I believe is unique. It's not like other firms that look to invest in the ideas of others and then set out to build companies. This is a fine and effective model. But we actually have our own laboratories and scientists, so we create new companies based on our ideas or ideas that emerge through collaborating with others. We won't start a project unless we believe it has the potential to transform some part of medicine. We only work on technology or biology platforms that can move into several therapeutic areas where there are many opportunities to have impact. That's in contrast to relying on a single lead com-

pound that might eventually become a drug. It's kind of a "reverse discovery." We begin with a problem and then figure out what's needed to address that problem.

For example, I'm involved with one Flagship company called Rubius, which focuses on using red blood cells to transport biologically important molecules around the body everywhere that blood goes. These cells could carry enzymes to treat phenylketonuria or immuno-oncology drugs, among many other possibilities. This is different than my initial experience in biopharmaceuticals where the focus was more singular, where single compounds were developed into drugs based on which enzyme could be inhibited or which receptor could be antagonized. Ideas like the one Rubius is developing start from a different place. I'm excited to be back on the learning curve and what I enjoy most is being able to contribute while also learning at the same time.

NU: Your description of Flagship makes it sound like an innovation lab in addition to a venture capital firm. Could you speak about the fit between you and Flagship, and how you apply things you learned from previous roles in Flagship's design process?

MR: Flagship now is almost 20 years old, and since I've only been with the firm for 2 years, I take very little credit for the achievements that they've had. However, a couple of years ago they consciously began to think about what they needed in terms of expertise and resources to do the best job of creating companies based on novel approaches to addressing disease. The core of Flagship is a talented group of scientist-entrepreneurs, people who can examine emerging science and figure out how it can be applied to be a commercial success. Surrounding that core of scientist-entrepreneurs is a ring of people who are seasoned in sectors that interface with biotechnology. I was hired as somebody who had considerable experience in clinical trials and in taking discovery from the lab and bringing it across the chasm into the clinic and eventually getting drugs approved in the United States and globally. At the same time, they hired David Epstein who ran Novartis and has real expertise in big pharma. We also brought in Steve Berenson, a previous vice chairman at J.P. Morgan who understands what's required to capitalize these companies adequately and what the sources of capital are. We brought in Jim Gilbert, whose expertise derives from experience with Boston Scientific and Bain & Company. These new additions to the Flagship team are helping the firm to move to a new level, which is especially important when you're making long-term commitments to companies.

When I started in this role, I entered thinking that I would mostly be involved during the design of clinical trials and looking at the results of the trials to remediate any issues. But since the early companies at Flagship can move in multiple directions, I wind up spending a lot of time, in addition, helping early stage companies decide which specialties in medicine are the best to apply their technology with the highest probability of success, as well as which therapeutic areas to avoid—diseases where pharmaceutical companies have been unsuccessful in the past. I'm spending time both at the earliest stage when these companies are being conceived and at the later stages once the technology that they are developing has made its way into the clinic.

NU: It's clear that you play a longitudinal and strategic role in the development of these ventures, especially when it comes to figuring out the medical niche that's most appropriate for these ideas. In doing this, it sounds like you're tapping into some of your previous work in industry and experience with academic medicine. In addition to employing these aspects of your background at Flagship, we've also seen you use them to comment on partnerships between sectors, especially on issues such as the reproducibility crisis in translational research and its impact on industry partners who are looking to commercialize drugs based on academic data that can't be replicated very easily. In a call to action that you issued previously, you mentioned that universities could invest in replicating research results. What is the importance of partnership between academia and industry, and how can such collaboration help address the reproducibility crisis?

MR: I think that collaboration between academia and industry is absolutely critical if we are to advance scientific and medical knowledge into new therapies. There is plenty of unmet medical need in many areas that can't be addressed by any single component of the health care ecosystem. We desperately need innovation in how we deliver care and in who delivers care. There's a special kind of innovation, which I call invention, which comes from biopharmaceutical companies that are absolutely reliant on academia, so we have to find a way to work together. Invention has to be done based on rigorous science that will hold up because you're going to be putting agents into human beings, which is potentially very dangerous. The database for starting a drug invention program should include data of high integrity. It's in every stakeholder's interest to ensure this high quality, not only because academia-industry collaboration can provide funding to a lab. Initiating an invention program with incorrect data can not only waste time and money but also create a big opportunity cost because that time and money could have been spent working on something that had a much higher probability of success. Data that can't be reproduced impacts the reputation of the NIH, which sponsors much of the research that produces this data, as well as the entire scientific enterprise. It is for these reasons that much has been written about this issue of irreproducibility of data, and people have offered many potential remedies.

I don't know if the remedy entails training graduate students in statistics, honor pledges, or courses on evaluating data. Rather than solving the problem, I hoped to offer a potential way to get data that's worthy of further investigation at the interface of academia and industry. One way to do it would be to offer incentives for "guaranteed" data. A university could guarantee that their data—the basis of their collaboration with a company—is reproducible. That would save time and money and prevent the loss of opportunities, as well as offer greater market value. In exchange, industry would pay more for guaranteed data than for data of unknown reliability, especially because industry is currently paying twice as much for all of its collaborations as it would pay if the data were reliable because roughly half the data is not reproducible. It doesn't necessarily require more investments by the university. The university could choose not to reproduce the data (if they have a very high level of confidence in the data before forming industry collaboration). But in order to obtain higher payments from industry, they must risk giving the money back if the data can't be reproduced. This hasn't been done yet, so this is still a "thought experiment." If one reputable university and one reputable biopharmaceutical company decided to try it as an experiment, we could have a better idea about whether it works in practice.

NU: Why do you think that no one has tried to pioneer this idea yet?

MR: I think that the impetus has to come from the university. It's hard for any one university to admit that this problem exists within its walls, despite knowing that the problem is widespread across many different fields and kinds of research institutions. Much of the irreproducibility problem is not because of the falsification of data or because of variability in techniques, but perhaps because of issues with statistical power, such as a study that should be powered with 20 animals is done with only eight animals. There could also be pressure added on faculty by the university that stands to gain twice as much money if the faculty can replicate their data. It can be complicated inside the university to make this kind of guarantee, but I could also argue that you should have that high level of confidence in your data or you have no right to be "selling" it into a collaboration.

NU: Along the lines of academia and industry trying to work together, we've also seen you talk about partnerships that allow for the sharing of electronic clinical data, such as the Merck-Regenstrief partnership. When it comes to the sharing of this type of data, how can guidelines be developed to address the conflicts of interest that critics believe unduly influence these relationships?

MR: I think these kinds of collaboration hold great promise. There are institutions and health care delivery systems like Regenstrief that have had high-quality clinical datasets for 30–40 years, and these contain information on the natural history of disease and the impact of various therapies on disease. These are uniquely valuable data for guiding a new drug discovery program and are also a natural basis for collaboration. Those health systems can not invent new medicines on their own, and pharmaceutical companies could never have access to this kind of data without collaborating with organizations like Regenstrief. Merck had a small number of these partnerships in other parts of the world. For instance, we partnered with a health system called Maccabi in Israel that has electronic, high-quality medical records spanning nearly a lifetime for certain patients.

In general, conflicts of interest in these areas aren't the biggest challenges because electronic record sharing won't influence prescribing patterns. The biggest challenges surround the protection of privacy and confidentiality of patient records. Hacking frequently affects banks and retailers and can certainly affect health systems. There is a lot of personal data that can hurt people if it enters into the public domain. This problem will only increase in importance as genetic data gets entered into clinical records because a person's genome is uniquely identifying and can even be used to identify relatives in the same database. Conflict of interest is still an important consideration, which is why I think it is time to settle on a satisfactory, stable, and workable set of conflict of interest principles. We're never going to make them perfect, but we can make them good enough to enable academia and industry to interact productively. As long as we have uncertainty about the rules governing the interface, we will inhibit these kinds of collaborations.

NU: Some might think that sharing electronic clinical data from health records may be similar to sharing electronic clinical trial data. We were wondering if you could discuss the similarities and differences between those two kinds of data sharing arrangements. Do you think that partnerships between researchers and companies can be developed to share clinical trial data in the same way that partnerships like the Merck-Regenstrief collaboration share health record data?

MR: Clinical trial data is different. When looking at clinical data in the health system, you can make observations about patients in the "real world." On the other hand, a clinical trial involves the testing of a new therapy in which a biopharmaceutical company or a device company has invested a lot of money. There's no question that this trial data should be made available at some point, but the question is when. If you make all of this data available too early, then you make it very easy for competitors to take advantage of the situation, which has a chilling effect on innovation. If you wait too long, you don't have the potential benefits of sharing clinical data. I think the most compelling case for the sharing of data from clinical trials is around the issue of safety. For example, if you are looking at a new potential drug in clinical trials that displays unexpected adverse effects or toxicity, it's hard to argue that such data on safety shouldn't be made widely available.

Proving efficacy is different. I don't think the argument is as compelling for making that urgently available. Although there's a lot of talk regarding the sharing of clinical trial data, it's actually hard to point to many examples where the sharing of clinical trial data has made new discoveries happen faster or revealed some new insight that wasn't known before. That's another reason that I think that clinical trial data sharing has a slower time point than sharing clinical data from health systems. I remember hearing that from the point of view of journal editors, the inquiries to journals to see the clinical trial data behind publications comes mostly from competitors and from lawyers, rather than from investigators in academia. Ten years ago, when we at Merck started making clinical trial data sets available, we noticed that few people asked for them. These considerations and trends make sharing clinical trial data different from sharing electronic health record data. When we start seeing benefits to sharing this type of data more readily, then sharing may

become more prominent, but for now, with the exception of safety data, trial data can be shared, but less urgently.

NU: To close, we were wondering if there are other insights or wisdom you'd like to impart to our readership in the medical community?

MR: I imagine that the people who attend Harvard Medical School are pluripotential, in that they're talented in many areas. Many people spend a lot of time thinking about juggling everything at once because they don't want to close any options. They want to do as many things as they can for as long as they can. It's important to remember that life and one's career are hopefully long, and that you don't have to do everything simultaneously. Instead, you can do things serially. You can spend part of your career as a laboratory researcher or clinician and spend another part of your career in clinical care delivery. That's another formula for keeping options open: doing things serially instead of in parallel.